

Supplemental Table S1: Strain phenotypes.

Strain	15mM Caffeine 1	15mM Caffeine 2	1M NaCl 1	1M NaCl 2
273614X_b	1.29	1.27	0.41	0.52
CBS2888_1b	1.77	1.66	0.28	0.41
CBS3093_1b	1.69	1.82	0.18	0.32
CBS7960_2	0.76	0.78	0.91	0.90
CECT10109_1b	0.51	0.60	0.89	1.07
CECT10266_1b	0.81	1.19	0.94	1.16
CEN.PK	0.38	0.39	0.06	0.06
CLIB154_1b	0.43	0.42	0.96	0.96
CLIB219_2b	0.51	0.41	0.13	0.09
CLIB272_2	0.75	0.82	1.31	1.83
CLIB274_1	0.93	1.21	0.19	0.42
CLIB294_1b	0.81	0.52	1.11	0.77
CLIB318_1	0.30	0.37	1.67	1.48
CLIB324_2	0.75	0.67	0.84	0.72
CLIB326_1	0.64	0.30	0.66	0.30
CLIB382_1b	0.50	0.40	1.01	0.90
CLIB413_1b	0.82	0.57	1.48	1.00
DBVPG1339_1b	0.23	0.25	1.27	1.01
DBVPG1788_1b	0.97	0.70	1.78	1.33
DBVPG1794_1b	0.75	0.57	1.78	1.30
DBVPG3591_1b	0.48	0.44	1.05	0.99
DBVPG4651_1b	0.45	0.45	0.37	0.32
DBVPG6861	0.46	0.44	0.83	0.85
EM93_3	0.54	0.49	0.78	0.74
FL200	0.75	0.77	0.77	0.70
FY5	0.62	0.66	1.09	1.21
I14_1b	0.70	0.77	1.30	1.37
IL_01_b	0.42	0.44	1.24	1.21
K1_1	0.20	0.19	0.83	0.97
K12_2	0.75	0.69	0.68	0.58
M22_1b	1.59	2.31	2.33	2.69
NC_02_b	1.36	1.27	0.07	0.07
PW5_b	0.44	0.45	0.05	0.05
RM11_1b	0.55	0.62	0.90	0.98
Sigma	1.23	1.03	0.14	0.15
SK1208	0.53	0.27	0.16	0.11
T7_b	1.19	1.15	0.38	0.37
T73_1b	0.72	0.73	1.08	1.07
UC1_1b	1.40	1.35	1.08	0.98
UC8_1b	0.67	0.65	1.23	1.21
WE372_1b	0.65	0.61	1.25	1.09
Y10_1b	0.08	0.08	0.25	0.21
Y12_b	0.62	0.64	0.90	0.85
Y3_1b	1.33	0.89	0.18	0.68
Y55_1b	1.39	1.20	2.91	0.51

Y9_4	0.47	0.43	0.99	0.89
Y9J_1b	0.99	1.02	0.51	0.60
YJM145_b	0.79	0.82	0.46	0.50
YJM269_1b	0.51	0.53	1.26	1.29
YJM280_b	0.34	0.42	0.42	0.35
YJM320_b	0.48	0.52	0.67	0.66
YJM326_b	2.04	2.17	0.51	0.60
YJM413_b	1.13	1.13	0.29	0.23
YJM421_1b	0.90	0.78	0.54	0.58
YJM428_1b	0.79	0.92	0.65	0.77
YJM434_1b	0.88	0.78	1.12	1.01
YJM436_1b	0.44	0.45	1.17	1.15
YJM440_1b	1.63	1.54	0.75	0.78
YJM454_1b	1.19	1.19	0.15	0.25
YJM653_1b	0.27	0.12	0.95	0.99
YJM678_1b	1.25	1.38	0.33	0.19
YJM981_b	0.52	0.70	1.39	1.74
YPS1000_1b	0.90	0.91	0.56	0.23
YPS1009_b	1.19	1.15	0.28	0.20
YPS163_1b	1.12	1.10	0.50	0.26

Each measurement is the average growth of four technical replicates adjusted for growth on YPD alone. The average of the two biological replicates is plotted in Figure 2A. Strains used in the round-robin cross are indicated in red.

Supplemental Table S2: Summary of RR segregant data and corresponding QTL patterns.

Cross	MATx	MATa	Segregants Salt	Epistasis test Salt	Salt QTL alleles	Segregants Caffeine	Epistasis test Caffeine	Caffeine QTL alleles
1	YPS1009	I14	Complex (negative)	5.65E-07	Complex (1 from each strain)	Complex (negative)	0.006	Complex (3 YPS1009, 1 I14)
2	Y10	I14	Bimodal	0.313	Bimodal (only ENA from I14)	Transgressive	0.981	Complex (5 I14 alleles)
3	Y10	PW5	Slight transgressive	0.880	Complex (2 from each strain)	Transgressive	0.875	Complex (1 Y10, 4 PW5)
4	PW5	273614X	Complex	0.775	Complex (1 PW5, 8 273614x)	Transgressive	0.021	Complex (1 from each)
5	YJM981	273614X	Bimodal	0.367	Complex (2 from each strain)	Complex	0.866	Complex (4 YJM981, 2 273614x)
6	YJM981	CBS2888	Complex (negative)	6.72E-05	Complex (4 YJM981, 1 CBS2888)	Complex	1.000	Complex (1 YJM981, 4 CBS2888)
7	CLIB219	CBS2888	ND	0.775	Complex (5 CLIB219, 8 CBS2888)	Nearly Bimodal	0.299	Bimodal (1 CBS2888)
8	M22	CLIB219	Transgressive	0.917	Complex (5 M22, 3 CLIB219)	Transgressive	0.608	Complex (1 M22, 4 CLIB219)
9	YJM269	M22	Transgressive	0.859	Complex (3 YJM269)	Transgressive	0.997	Complex (1 YJM269, 2 M22)
10	NC-02	YJM269	Complex (negative)	0.602	Complex (2 NC-02, 5 YJM269)	Transgressive	0.970	Complex (4 NC-02, 3 YJM269)
11	NC-02	YJM454	ND	0.880	Complex (4 NC-02, 5 YJM454)	Unimodal	0.857	Bimodal (1 YJM454)
12	YPS1009	YJM454	ND	0.300	Complex (1 YPS1009, 8 YJM454)	Unimodal	0.291	None

Significant Epistasis scores

Supplemental Table S3: Replicate confirmed BY/RM QTL.

QTL	Condition	Chromosome	LOD score	Max LOD position	Lower bound of QTL	Upper bound of QTL	Replicate Pairs
Caff.chr01.1	15mM Caffeine	chr01	6.83	34500	16450	52550	4
Caff.chr04.1	15mM Caffeine	chr04	6.25	371625	335950	411600	4
Caff.chr04.2	15mM Caffeine	chr04	8.75	594125	565375	624725	4
Caff.chr08.1	15mM Caffeine	chr08	13.51	174625	159825	190750	4
Caff.chr11.1	15mM Caffeine	chr11	50.85	57675	52375	63675	4
Caff.chr12.1	15mM Caffeine	chr12	7.75	470275	446450	498700	4
Caff.chr13.1	15mM Caffeine	chr13	20.31	245500	233500	278525	4
Caff.chr14.1	15mM Caffeine	chr14	55.88	472725	463975	481850	4
Caff.chr15.1	15mM Caffeine	chr15	7.01	74875	48325	102050	4
Caff.chr15.2	15mM Caffeine	chr15	22.97	625325	615775	636200	4
NaCl.chr09.1	1M NaCl	chr09	7.06	117700	86525	153525	4
NaCl.chr14.1	0.5M & 1M NaCl	chr14	19.32	376000	359675	388975	6

QTL that passed a LOD score threshold of 5 and were identified in at least one pair of technical replicates are listed.

Supplemental Table S4: Grouped RR QTL

Condition	QTL	Chromosome	LOD score	Max LOD position	Lower bound of QTL	Upper bound of QTL	Crosses with QTL	# Crosses with QTL	Number of Coding Variants in QTL	Significant Variants	Association Score Coding Variants	Association Score All Variants	Candidate QTG
Caffeine	Caff.chr03.1	chr03	8.22	288775	267550	291500	8	1	109	13	0.535	0.535	
	Caff.chr04.1	chr04	6.06	463300	442650	502800	1	1	155	13	0.628	0.628	
	Caff.chr04.2	chr04	38.12	877925	866200	896475	2,3	2	48	4	0.999	0.999	MSS4
	Caff.chr07.1	chr07	8.04	513400	468500	567450	2,3	2	221	28	0.762	0.762	MSB2,MTL1,GSC2
	Caff.chr08.1	chr08	14.76	25675	18175	41725	5	1	83	7	0.507	0.507	GUT1,VMR1
	Caff.chr08.2	chr08	8.53	178850	133700	207650	10	1	221	23	0.517	0.517	SLT2
	Caff.chr09.1	chr09	5.58	412900	397400	413000	5	1	60	2	0.992	0.992	
	Caff.chr10.1	chr10	29.08	561025	547725	569800	1,2,3,5,6,8,9,10	8	77	4	0.349	0.356	TOR1 (confirmed)
	Caff.chr10.2	chr10	28.77	459000	431300	477200	5,6	2	112	3	0.793	0.793	CYR1
	Caff.chr11.1	chr11	10.81	59650	46400	73900	1,2,3,6,11	5	79	2	0.320	0.371	TOR2
	Caff.chr11.2	chr11	7.23	633650	613500	634000	4,5	2	70	3	0.690	0.690	
	Caff.chr12.1	chr12	9.44	653850	614300	682850	9	1	183	15	0.501	0.501	HAP1,GSY2
	Caff.chr12.2	chr12	6.90	460250	446550	484850	10	1	5	0	0.128	0.794	
	Caff.chr13.1	chr13	10.07	26975	14900	51250	10	1	124	12	0.315	0.445	RSC9,ATR1,GTR1
	Caff.chr14.1	chr14	5.65	227800	207250	276150	1	1	232	12	0.320	0.617	
	Caff.chr14.2	chr14	19.63	468650	453125	482700	10	1	96	10	0.426	0.535	
	Caff.chr15.1	chr15	8.61	625275	604100	648050	2,4,9,10	4	139	2	0.413	0.413	PDR5
	Caff.chr15.2	chr15	8.42	45200	40650	49150	3	1	32	2	0.291	0.506	
	Caff.chr15.3	chr15	38.56	406200	395000	421500	5,7,8	3	107	8	0.778	0.778	WHI2 (confirmed)
	Caff.chr15.4	chr15	8.94	136725	115125	163375	6	1	166	17	0.409	0.409	WSC3,PKH2
	Caff.chr15.5	chr15	7.44	1005250	978600	1033900	10	1	175	13	0.358	0.502	
	Caff.chr16.1	chr16	21.14	416875	389900	435400	6,8	2	130	8	0.428	0.996	BRO1,RGL1
	Caff.chr16.2	chr16	6.85	208000	187200	236800	8	1	209	8	0.777	0.777	TCO89
NaCl	NaCl.chr02.1	chr02	11.84	538250	510450	567050	10,11,12	3	203	5	0.841	0.841	IRA1
	NaCl.chr02.2	chr02	6.47	238950	189950	269050	11	1	227	12	0.483	0.483	
	NaCl.chr03.1	chr03	5.62	33600	14900	54750	7	1	111	0	0.243	0.360	
	NaCl.chr03.2	chr03	6.55	289800	263700	291500	8	1	124	5	0.351	0.351	
	NaCl.chr04.1	chr04	41.24	509600	491650	531850	1,2,3,5,6,7,8,9,10,11,12	11	51	0	0.180	0.465	ENA locus
	NaCl.chr04.2	chr04	18.21	421750	411600	429050	3	1	48	1	0.235	0.574	GPD1
	NaCl.chr04.3	chr04	6.05	192600	142400	230050	7	1	229	22	0.476	0.830	
	NaCl.chr04.4	chr04	9.00	834700	797100	861150	7	1	190	0	0.217	0.452	
	NaCl.chr04.5	chr04	6.55	1397800	1368600	1412700	7	1	113	13	0.538	0.538	
	NaCl.chr05.1	chr05	15.35	107825	81750	133825	4	1	162	0	0.454	0.454	
	NaCl.chr05.2	chr05	8.21	514325	493975	546450	4,7	2	168	0	0.306	0.471	BCK2
	NaCl.chr05.3	chr05	9.87	418800	387600	441000	12	1	141	10	0.414	0.604	SHO1
	NaCl.chr07.1	chr07	10.67	932050	898400	958400	4,5,7	3	195	14	0.504	0.504	
	NaCl.chr07.2	chr07	8.20	536050	511300	571500	4,6,11	3	104	5	0.406	0.406	MSB2,MTL1,GSC2
	NaCl.chr07.3	chr07	6.20	15000	14900	22300	7	1	11	0	0.113	0.337	
	NaCl.chr08.1	chr08	13.02	51250	27250	65125	4,5,10	3	171	10	0.829	0.829	GUT1,WSC4,VMR1
	NaCl.chr10.1	chr10	8.93	548300	530050	561300	3,4	2	108	10	0.727	0.727	OSM1,STK2
	NaCl.chr10.2	chr10	28.50	434650	420250	451625	5,6	2	81	4	0.888	0.888	CYR1
	NaCl.chr10.3	chr10	21.11	204725	182800	234375	6,10	2	143	2	0.476	0.476	YJL107c & YJL108c
	NaCl.chr10.4	chr10	6.09	104300	78050	150900	9	1	221	23	0.500	0.500	
	NaCl.chr10.5	chr10	6.52	37400	14900	53550	11	1	117	4	0.422	0.488	
	NaCl.chr11.1	chr11	12.84	66850	49425	78250	8,10,11	3	86	5	0.368	0.636	TOR2
	NaCl.chr11.2	chr11	5.46	598050	542750	639900	9	1	355	13	0.484	0.494	
	NaCl.chr11.3	chr11	7.24	237750	206100	262650	10	1	204	8	0.563	0.606	
	NaCl.chr12.1	chr12	10.72	872550	854850	891450	7	1	99	0	0.430	0.465	
	NaCl.chr12.2	chr12	13.79	457350	428400	475850	12	1	84	10	0.671	0.671	
	NaCl.chr13.1	chr13	8.09	288300	255700	338200	3,4,12	3	252	2	0.689	0.689	
	NaCl.chr13.2	chr13	6.35	571100	532600	615800	4	1	314	17	0.406	0.409	
	NaCl.chr13.3	chr13	15.45	706900	671575	720300	7,11	2	216	12	0.420	0.420	EFR3
	NaCl.chr14.1	chr14	8.01	582200	550350	605000	4,8,12	3	92	2	0.555	0.555	CRZ1
	NaCl.chr14.2	chr14	6.28	139400	132300	145900	11	1	39	1	0.337	0.922	
	NaCl.chr14.3	chr14	10.61	263050	225900	299900	12	1	240	28	0.438	0.438	
	NaCl.chr15.1	chr15	21.98	73800	57650	87150	6,11,12	3	81	3	0.311	0.416	YGK3
	NaCl.chr15.2	chr15	57.10	408100	398850	412700	7,8,12	3	64	4	0.939	0.939	WHI2 (confirmed)
	NaCl.chr15.3	chr15	9.67	1020100	992200	1042025	8,10	2	143	9	0.478	0.856	PDE2
	NaCl.chr16.1	chr16	6.81	434250	399150	481050	1,7,8	3	213	0	0.628	0.628	
	NaCl.chr16.2	chr16	43.89	206950	206625	212175	7,8	2	47	6	0.922	0.922	TCO89,RTT10

Legend

QTL	QTL identifier
LOD score	Combined LOD score of grouped QTL
Max LOD position	Position with highest LOD score across grouped QTL
Crosses with QTL	Round-robin crosses in which the QTL was detected
Lower/upper bound of QTL	2-LOD confidence interval of QTL
Number of Coding Variants in QTL	Non-synonymous coding variants within the QTL interval across the RR parent strains
Significant Variants	Number of non-synonymous coding variants with a significant association score
Association Score	
Coding Variants	Maximum association score among non-synonymous coding variants
Association Score	
All Variants	Maximum association score among all variants within the QTL interval
Candidate QTG	Candidate quantitative trait genes based on Saccharomyces Genome Database gene annotations

GOID	GO_term
16740	transferase activity

GOLD ID	GO_term transferrase activity	Cluster frequency 128 out of 851 genes, 15.0%	Background frequency 741 out of 7167 background genes, 10.3%	P-value 0.00113	FDR 0	Expected FP 0	Gene(s) annotated to the term
16740	transferrase activity						<p>0 ALK2/YBL009W:SC11/YBL011W:FMT1/YBL013W:FUS3/YBL016W:RER2/YBR002C:COQ1/YBR003W:GPI18/YBR004C:MNN2/YBR015C:MCK1/YBR136W:BMT2/YBR141C:CSH1/YBR16W:GLK1/YCL040W:APJ1/YCL052C:SPB1/YCL054W:KIN82/YCR091W:NOP1/YDL014W:CDC7/YDR123W:LYS21/YDL131W:RP021/YDL140C:CRD3/YDL142C:RPCF3/YDL150W:STE7/YDL159W:AIR2/YDL175C:ARO3/YDR035W:ARG82/YDR173C:NGG1/YDR176W:SAS4/YDR181C:CAB5/YDR196C:RKM2/YDR198C:PPA5/YDR459C:RMT2/YDR465C:PKH3/YDR466W:SDC1/YDR469W:SNF1/YDR477W:GLC3/YEL011W:BUD16/YEL029C:YCK3/YER123W:SAK1/YER129W:CGG1/YER163C:CCA1/YER168C:ADK2/YER170W:TMT1/YER175C:NMA2/YGR010W:UGA1/YGR019W:THG1/YRH024C:GSC2/YMR23W:PMT6/YGR199W:PC11/YGR202C:YCH1/YGR203W:SLI1/YGR212W:GPI1/YGR216C:DIE2/YGR227W:GUT1/YHL032C:CTK2/CTK2/YL006C:IME2/YLI06W:YAK1/YLI41C:TPK1/YLI164C:HAL5/YLI187C:CDG8/YR025W:PTK2/YJR059W:TOR1/YR066W:HSL1/YKL116C:YPK1/YKL126W:PTK1/YKL198C:TOR2/YKL203C:CDG5/YMR001C:SEC59/YMR13C:RIM11/YMR139W:PFK2/YMR205C:ERG12/YMR208W:SKY1/YMR215W:SGK3/YOL125W:YGK3/YOL128C:GA54/YOL132W:YLI192W:RIO2/YNL207W:ALG5/YNL219C:PIK1/YNL267W:LTM13/YNL24C:TRM13/YOL125W:YGK3/YOL128C:GA54/YOL132W:PFK22/YOL136C:ARG8/YOL140W:PPM2/YOL141W:MEK1/YOR351C:MR56/YOR370C:SSN3/YPL042C:MNN9/YPL050C:KTR8/YPL053C:SUR1/YPL057C:BTS1/YPL069C:GPI2/YPL076W</p>
16301	kinase activity	46 out of 851 genes, 5.4%	200 out of 7167 background genes, 2.8%	0.00205	0	0	<p>0 ALK2/YBL009W:FUS3/YBL016W:MCK1/YBR136W:GLK1/YCL040W:KIN82/YCR091W:CDG7/YDL017W:STE7/YDL159W:ARG82/YDR173C:CAB5/YDR196C:PKH3/YDR466W:SNF1/YDR477W:BUD16/YEL029C:YCK3/YER123W:SAK1/YER129W:GUT1/YHL032C:CTK2/YL006C:IME2/YLI06W:YAK1/YLI41C:TPK1/YLI164C:HAL5/YLI187C:CDG8/YR025W:PTK2/YJR059W:TOR1/YR066W:HSL1/YKL116C:YPK1/YKL126W:PTK1/YKL198C:TOR2/YKL203C:CDG5/YMR001C:SEC59/YMR13C:RIM11/YMR139W:PFK2/YMR205C:ERG12/YMR208W:SKY1/YMR216C:ERG8/YMR220W:MRE11/YMR224C:ARK1/YNL020C:NPR1/YNL183C:DUO3/YNL191W:CHS1/YNL192W:RIO2/YNL207W:ALG5/YNL219C:PIK1/YNL267W:LTM13/YNL24C:TRM13/YOL125W:YGK3/YOL128C:GA54/YOL132W:PFK22/YOL136C:ARG8/YOL140W:PPM2/YOL141W:MEK1/YOR351C:MR56/YOR370C:SSN3/YPL042C:MNN9/YPL050C:KTR8/YPL053C:SUR1/YPL057C:BTS1/YPL069C:GPI2/YPL076W</p>
16773	phosphotransferase activity, alcohol group as acceptor	42 out of 851 genes, 4.9%	178 out of 7167 background genes, 2.5%	0.00266	0	0	<p>0 ALK2/YBL009W:FUS3/YBL016W:MCK1/YBR136W:GLK1/YCL040W:KIN82/YCR091W:CDG7/YDL017W:STE7/YDL159W:ARG82/YDR173C:CAB5/YDR196C:PKH3/YDR466W:SNF1/YDR477W:BUD16/YEL029C:YCK3/YER123W:SAK1/YER129W:GUT1/YHL032C:CTK2/YL006C:IME2/YLI06W:YAK1/YLI41C:TPK1/YLI164C:HAL5/YLI187C:CDG8/YR025W:PTK2/YJR059W:TOR1/YR066W:HSL1/YKL116C:YPK1/YKL126W:PTK1/YKL198C:TOR2/YKL203C:CDG5/YMR001C:SEC59/YMR13C:RIM11/YMR139W:PFK2/YMR205C:ERG12/YMR208W:SKY1/YMR216C:ERG8/YMR220W:MRE11/YMR224C:ARK1/YNL020C:NPR1/YNL183C:RIO2/YNL207W:PIK1/YNL267W:YGK3/YOL128C:MEK1/YOR351C:SSN3/YPL042C</p>
16773	phosphotransferase activity, alcohol group as acceptor	42 out of 851 genes, 4.9%	178 out of 7167 background genes, 2.5%	0.00266	0	0	<p>0 ALK2/YBL009W:FUS3/YBL016W:MCK1/YBR136W:GLK1/YCL040W:KIN82/YCR091W:CDG7/YDL017W:STE7/YDL159W:ARG82/YDR173C:CAB5/YDR196C:PKH3/YDR466W:SNF1/YDR477W:BUD16/YEL029C:YCK3/YER123W:SAK1/YER129W:GUT1/YHL032C:CTK2/YL006C:IME2/YLI06W:YAK1/YLI41C:TPK1/YLI164C:HAL5/YLI187C:CDG8/YR025W:PTK2/YJR059W:TOR1/YR066W:HSL1/YKL116C:YPK1/YKL126W:PTK1/YKL198C:TOR2/YKL203C:CDG5/YMR001C:SEC59/YMR13C:RIM11/YMR139W:PFK2/YMR205C:ERG12/YMR208W:SKY1/YMR216C:ERG8/YMR220W:MRE11/YMR224C:ARK1/YNL020C:NPR1/YNL183C:RIO2/YNL207W:PIK1/YNL267W:YGK3/YOL128C:MEK1/YOR351C:SSN3/YPL042C</p>
4672	protein kinase activity	32 out of 851 genes, 3.8%	132 out of 7167 background genes, 1.8%	0.01849	0	0	<p>0 ALK2/YBL009W:FUS3/YBL016W:MCK1/YBR136W:KIN82/YCR091W:CDG7/YDL017W:STE7/YDL159W:PKH3/YDR466W:SNF1/YDR477W:YCK3/YER123W:SAK1/YER129W:CTK2/YL006C:IME2/YLI06W:YAK1/YLI41C:TPK1/YLI164C:HAL5/YLI165C:SWEI/YML187C:PTK2/YJR059W:TOR1/YR066W:HSL1/YKL101W:PRR1/YKL116C:YPK1/YKL126W:PTK1/YKL198C:TOR2/YKL203C:CDG5/YMR001C:SEC59/YMR13C:RIM11/YMR139W:PFK2/YMR205C:ERG12/YMR208W:SKY1/YMR216C:ERG8/YMR220W:MRE11/YMR224C:ARK1/YNL020C:NPR1/YNL183C:RIO2/YNL207W:YGK3/YOL128C:MEK1/YOR351C:SSN3/YPL042C</p>
16758	transferase activity, transferring hexosyl groups	22 out of 851 genes, 2.6%	80 out of 7167 background genes, 1.1%	0.03874	0	0	<p>0 GPI18/YBR004C:MNN2/YBR015C:CSH1/YBR161W:PBH1/YCL052C:GLC3/YEL011W:GSC2/YGR032W:PMT6/YGR199W:GPI1/YGR216C:DIE2/YGR227W:GUT1/YHL032C:CTK2/CTK2/YL006C:IME2/YLI06W:YAK1/YLI41C:TPK1/YLI164C:HAL5/YLI165C:SWEI/YML187C:PTK2/YJR059W:TOR1/YR066W:HSL1/YKL101W:PRR1/YKL116C:YPK1/YKL126W:PTK1/YKL198C:TOR2/YKL203C:CDG5/YMR001C:SEC59/YMR13C:RIM11/YMR139W:PFK2/YMR205C:ERG12/YMR208W:SKY1/YMR216C:ERG8/YMR220W:MRE11/YMR224C:ARK1/YNL020C:NPR1/YNL183C:RIO2/YNL207W:PIK1/YNL267W:YGK3/YOL128C:MEK1/YOR351C:SSN3/YPL042C</p>

GOID	GO_term
51716	cellular response to stimulus

GOID	GO_term	Cluster frequency	Background frequency	P-value	FDR	Expected FP	Gene(s) annotated to the term
51716	cellular response to stimulus	134 out of 851 genes, 15.7%	788 out of 7167 background genes, 11.0%	0.00614	0	0	<p>PDR3/YBL005W:FUS3/YBL016W:UGA2/YBR006W:HHT1/YBR010W:GRX7/YBR014C:MEC1/YBR136W:IRA1/YBR140C:KAR4/YCL055W:FYV5/YCL058C:ATG1/YCL058W-</p> <p>A:MRJ1/YCL061C:G1G2/YCR089W:MSH3/YCR092C:CCD39/YCR093W:CDG7/YDL017W:RPM4/YDL020C:GPD1/YDL022W:RGT7/YDL138W:ATG9/YDL149W:STE7/YDL159W:CCD9/YDL164C:CCD36/YDL165W:FAP7/YDL166C:UGA3/YDL170W:REG1/YDR028C:RAD28/YDR030C:SEC7/YDR170C:CSN9/YDR179C:SCC2/YDR180W:DCD1/YDR182W:PLP1/YDR183W:NUP4/YDR192C:VP564/YDR200C:TFB3/YDR460W:MFA1/YDR461W:PKH3/YDR466W:SNF1/YDR477W:VAC8/YEL013W:EA5F/YEL018W:MMS21/YEL019C:GEA2/YEL022W:MCM3/YEL032W:BOI2/YER114C:SLX8/YER116C:SHO1/YER118C:DSE1/YER124C:RSP5/YER125W:RAD4/YER162C:RAD3/YER171W:RAD24/YER173W:GRX4/YER174C:BMH1/YER177W:MSB2/YGR014W:MTL1/YGR023W:ERV1/YGR029W:ZPP6/YGR211W:WNR3/YHL023C:SNR1/YHL025W:RIM101/YHL043C:CYR1/YL005W:GZF3/YL110C:ASF1/YL115W:SPT10/YL127C:PAR1/YL157C:TRK1/YL164C:RFA3/YL173C:SMW3/YL176C:ATG27/YL178C:SAG1/YR004C:POL31/YR006W:OSM1/YR051W:RAD7/YR052W:CBF1/YR060W:TOR1/YR066W:SLD2/YKL108W:HAP4/YKL109W:ABF1/YKL112W:RAD7/YKL113C:APN1/YKL114C:PRR1/YKL116C:TOR2/YKL203C:TRM2/YKR056W:OAF3/YKR064W:CCP1/YKR066C:NUP133/YKR082W:PXJ1/YKR090W:PC1/YKR095W-</p> <p>A:PCD1/YLR151C:ROM2/YLR371W:PSY3/YLR376C:SMC6/YLR383W:GIS4/YML006C:CSY1/YMR025W:TA42/YMR028W:FAR8/YMR029C:RSF1/YMR030W:HOF1/YMR032W:PSO2/YMR137C:SI5P/YMR140W:YIM1/YMR152W:TPP1/YMR156C:ATG16/YMR159C:MLH1/YMR167W:HOT1/YMR172W:DIS6/YMR175W:ECM5/YMR218C:MR5130/YMR218C:MR5130/YMR224C:SNB8/YML025C:CKZ1/YNL027W:WTL2/YNL031C:INE103/YNL036W:RHO5/YNL180C:YNL190W:PSY2/YNL201W:MMS1/YNL218W:ATG4/YNL223W:CKB2/YOR039W:SGO3/YOR353C:HAP5/YOR358W:PDE2/YOR360C:PI2P/YOR363C:RAD17/YOR368W:MR56/YOR370C:GPB1/YOR371C:SSN3/YPL042C:ELC1/YPL046C:DIG1/YPL049C:GRX5/YPL059W:GCR1/YPL075W:TCO89/YPL180W</p>
50896	response to stimulus	151 out of 851 genes, 17.7%	941 out of 7167 background genes, 13.1%	0.03891	0	0	

GOID	GO_term
404	loop DNA binding

GOID	GO term	Cluster frequency	Background frequency	P-value	FDR	Expected FP	Gene(s) annotated to the term
404	loop DNA binding	4 out of 461 genes, 0.9%	5 out of 7167 background genes, 0.1%	0.02174	0	0	MSH3/YCR092C:NHP10/YDL002C:PMS1/YNL082W:MSH2/YOL090W

GOID	GO_term	Cluster frequency	Background frequency	P-value	FDR	Expected FP	Gene(s) annotated to the term
50896	response to stimulus	89 out of 461 genes, 19.3%	941 out of 7167 background genes, 13.1%	0.07729	0.04	0.04	FIG2/YCR089W:KIN82/YCR091W:MSH3/YCR092C:CDC39/YCR093W:NHP10/YDL002C:MCD1/YDL003W:RAD57/YDR004W:SOK1/YDR006C:GAL3/YDR009W:SNQ2/YDR011W:PSF1/YDR013W:REG1/YDR028C:RAD28/YDR030C:UME6/YDR207C:UPC2/YDR213W:AH11/YDR214W:ADR1/YDR216W:PDR1/YGL013C:SWC4/YGR002C:STF2/YGR008C:MSB2/YGR014W:MTL1/YGR023W:ERV1/YGR029W:ORM1/YGR038W:SBP1/YHL034C:VMR1/YHL035C:YH19/YHR029C:SLT2/YHR030C:SRB2/YHR041C:YHK8/YHR048W:DAL81/YIR023W:YVH1/YIR026C:SAG1/YJR004C:POL31/YJR006W:CBF1/YJR060W:TOR1/YJR066W:RFC2/YJR068W:MNN4/YKL201C:TOR2/YKL203C:PCC1/YKR095W-A:FAR10/YLR238W:IRC20/YLR247C:RCK2/YLR248W:HAP1/YLR256W:LCB5/YLR260W:NEJ1/YLR265C:PDR8/YLR266C:ATR1/YML116W:GTR1/YML121W:RSC9/YML127W:EOS1/YNL080C:PMS1/YNL082W:MKT1/YNL085W:RHO2/YNL090W:NTS1/YNL091W:PSY2/YNL201C:RAP1/YNL216W:MGS1/YNL218W:ATG4/YNL223W:URE2/YNL229C:PDR16/YNL231C:MHF1/YOL086W-A:HAL9/YOL089C:MSH2/YOL090W:RFC4/YOL094C:PKH2/YOL100W:WSC3/YOL105C:SPT20/YOL148C:CKB2/YOR039W:WHI2/YOR043W:STD1/YOR047C:ELG1/YOR144C:PDR5/YOR153W:YRR1/YOR162C:REV1/YOR346W:SOG2/YOR353C:HAP5/YOR358W:PDE2/YOR360C:PIP2/YOR363C:RAD17/YOR368W:MRS6/YOR370C:GPB1/YOR371C:ALD6/YPL061W:GCR1/YPL075W:BRO1/YPL084W:REV3/YPL167C:TCO89/YPL180W:MF(ALPHA)1/YPL187W:POSS/YPL188W

Supplemental Table S6: Copy number of *ENA* variants in the round-robin parent strains.

Strain	chrIV coverage	ENA2 coverage	ENA2 copy number	ENA6 coverage	ENA6 copy number
YPS1009	70	0	0.00	6	0.09
I14	73	173	2.37	20	0.27
Y10	216	2	0.01	214	0.99
PW5	421	3	0.01	382	0.91
273614x	182	348	1.91	4	0.02
YJM981	173	1007.5	5.82	76	0.44
CBS2888	31	2	0.06	24	0.77
Clib219	143	1	0.01	103	0.72
M22	41	68	1.66	1	0.02
YJM269	120	197	1.64	2	0.02
NC-02	61	3	0.05	47	0.77
YJM454	179	2	0.01	142	0.79

For each strain, sequences were aligned to the coding sequence of *ENA2* (Sacharomyces Genome Database S288c YDR039c) or *ENA6* (GenBank: FJ228230.1). In order to determine their copy number of the *ENA* variants, we calculated the median sequencing coverage of these two variants and compared it to the median coverage of chromosome IV, on which both genes are located.

Supplemental Table S7: Alleles underlying round-robin QTL.

Strain information

Strain	Subgroup	Source
YPS1009	Nature	Oak exudate, New Jersey, USA
I14	Vineyard/Wine	Vineyard soil sample, Petrina, Italy
Y10	Nature	From a coconut in the Phillipines
PW5	Fermentation/Wine	Raphia Palm tree, Aba, Abia state, Nigeria
273614x	Clinical isolate	Newcastle, UK
YJM981	Clinical isolate	Bergamo, Italy
CBS2888	Soil	South Africa
CLIB219	Vineyard/Wine	Russia
M22	Vineyard/Wine	Vineyard, Italy
YJM269	Vineyard/Wine	From Blauer Portugieser grapes, Germany
NC-02	Nature	Oak exudate, North Carolina, USA
YJM454	Clinical isolate	USA

Alleles identified for each grouped QTL

QTL	Strains with beneficial alleles	Count	Strains with deleterious alleles	Count
Caff.chr03.1	CLIB219	1	M22	1
Caff.chr04.1	YPS1009	1	I14	1
Caff.chr04.2	I14,PW5	2	Y10	1
Caff.chr07.1	I14,PW5	2	Y10	1
Caff.chr08.1	YJM981	1	273614X	1
Caff.chr08.2	NC-02	1	YJM269	1
Caff.chr09.1	YJM981	1	273614X	1
Caff.chr10.1	YPS1009,I14,PW5,273614X,CBS2888,CLIB219,YJM269,NC-02	8	I14,Y10,YJM981,M22,YJM269	5
Caff.chr10.2	273614X,CBS2888	2	YJM981	1
Caff.chr11.1	I14,PW5,YJM981,YJM454	4	YPS1009,Y10,CBS2888,NC-02	4
Caff.chr11.2	PW5,YJM981	2	273614X	1
Caff.chr12.1	M22	1	YJM269	1
Caff.chr12.2	YJM269	1	NC-02	1
Caff.chr13.1	NC-02	1	YJM269	1
Caff.chr14.1	YPS1009	1	I14	1
Caff.chr14.2	YJM269	1	NC-02	1
Caff.chr15.1	I14,273614X,M22,NC-02	4	Y10,PW5,YJM269	3
Caff.chr15.2	Y10	1	PW5	1
Caff.chr15.3	YJM981,CBS2888,M22	3	273614X,CLIB219	2
Caff.chr15.4	CBS2888	1	YJM981	1
Caff.chr15.5	YJM269	1	NC-02	1
Caff.chr16.1	CBS2888,CLIB219	2	YJM981,M22	2
Caff.chr16.2	CLIB219	1	M22	1
NaCl.chr02.1	NC-02,YPS1009	2	YJM269,YJM454	2
NaCl.chr02.2	NC-02	1	YJM454	1
NaCl.chr03.1	CBS2888	1	CLIB219	1

NaCl.chr03.2	CLIB219	1	M22	1
NaCl.chr04.1	I14,PW5,YJM981,CLIB219,M22,YJM269,YJM454	7	YPS1009,Y10,273614X,CBS2888,CLIB219,M22,NC-02	7
NaCl.chr04.2	PW5	1	Y10	1
NaCl.chr04.3	CBS2888	1	CLIB219	1
NaCl.chr04.4	CLIB219	1	CBS2888	1
NaCl.chr04.5	CBS2888	1	CLIB219	1
NaCl.chr05.1	273614X	1	PW5	1
NaCl.chr05.2	273614X,CBS2888	2	PW5,CLIB219	2
NaCl.chr05.3	YJM454	1	YPS1009	1
NaCl.chr07.1	273614X,CBS2888	2	PW5,YJM981,CLIB219	3
NaCl.chr07.2	273614X,YJM981,NC-02	3	PW5,CBS2888,YJM454	3
NaCl.chr07.3	CBS2888	1	CLIB219	1
NaCl.chr08.1	PW5,YJM981,NC-02	3	273614X,YJM269	2
NaCl.chr10.1	Y10,273614X	2	PW5	1
NaCl.chr10.2	273614X,CBS2888	2	YJM981	1
NaCl.chr10.3	YJM981,YJM269	2	CBS2888,NC-02	2
NaCl.chr10.4	YJM269	1	M22	1
NaCl.chr10.5	YJM454	1	NC-02	1
NaCl.chr11.1	M22,YJM269,YJM454	3	CLIB219,NC-02	2
NaCl.chr11.2	YJM269	1	M22	1
NaCl.chr11.3	YJM269	1	NC-02	1
NaCl.chr12.1	CLIB219	1	CBS2888	1
NaCl.chr12.2	YJM454	1	YPS1009	1
NaCl.chr13.1	Y10,273614X,YJM454	3	PW5,YPS1009	2
NaCl.chr13.2	273614X	1	PW5	1
NaCl.chr13.3	CBS2888,NC-02	2	CLIB219,YJM454	2
NaCl.chr14.1	273614X,M22,YJM454	3	PW5,CLIB219,YPS1009	3
NaCl.chr14.2	YJM454	1	NC-02	1
NaCl.chr14.3	YJM454	1	YPS1009	1
NaCl.chr15.1	YJM981,YJM454	2	CBS2888,NC-02,YPS1009	3
NaCl.chr15.2	CBS2888,M22,YJM454	3	CLIB219,YPS1009	2
NaCl.chr15.3	M22,YJM269	2	CLIB219,NC-02	2
NaCl.chr16.1	YPS1009,CLIB219	2	I14,CBS2888,M22	3
NaCl.chr16.2	CLIB219	1	CBS2888,M22	2

For each instance of a QTL we determined whether each of the two strains involved in the corresponding cross contributed the beneficial or deleterious allele based on the allele frequency skews post selection.

Supplemental Table S8: Round-robin mating type dependent QTL.

Cross	Condition	Chromosome	LOD score	Max LOD position	Lower bound of QTL	Upper bound of QTL	Candidate QTG
Cross 2	YPD	chr12	8.8	1040100	1027900	1051000	SST2
Cross 2	1M NaCl	chr12	8.23	1041700	1026000	1050600	SST2
Cross 2	15mM Caffeine	chr12	6.27	1045100	1021500	1050600	SST2
Cross 2	20mM Caffeine	chr12	5.81	1049800	987900	1051000	SST2
Cross 3	0.5M NaCl	chr04	9.49	884100	855600	907000	MSS4
Cross 4	0.5M NaCl	chr12	12.3	18800	14900	25300	
Cross 4	1M NaCl	chr04	6.89	364800	343300	392800	
Cross 4	1M NaCl	chr12	6.58	15000	14900	31600	
Cross 4	1M NaCl	chr15	9.14	420900	304500	443300	
Cross 5	YPD	chr08	6.12	109300	84300	140100	GPA1
Cross 5	1M NaCl	chr08	6.75	101300	14900	146400	GPA1
Cross 5	20mM Caffeine	chr08	7.43	108800	89400	140400	GPA1
Cross 8	YPD	chr06	9.46	18200	14900	23300	
Cross 8	YPD	chr08	11.85	31100	19100	51800	
Cross 8	YPD	chr16	6.19	399000	377500	422700	
Cross 8	15mM Caffeine	chr11	7.68	65400	54700	74200	TOR2
Cross 8	20mM Caffeine	chr11	7.04	62800	49800	72900	TOR2
Cross 9	20mM Caffeine	chr08	5.01	45100	14900	80600	
Cross 10	YPD	chr08	8.58	94200	80300	121900	GPA1
Cross 10	1M NaCl	chr08	5.87	105400	87000	120700	GPA1
Cross 10	15mM Caffeine	chr08	7.58	93900	83500	103900	GPA1
Cross 10	15mM Caffeine	chr13	5.62	41500	14900	78900	
Cross 10	20mM Caffeine	chr08	5.67	94100	73300	122900	GPA1
Cross 10	20mM Caffeine	chr13	5.84	58900	14900	90200	
Cross 11	0.5M NaCl	chr07	8.4	104900	63400	122400	

QTL identified in multiple conditions are indicated in green. We excluded the 1M sodium chloride (NaCl) selections for Cross 11 from this analysis as this selection was stringent for this cross and few cells grew under this condition. While comparison of the MAT α and MAT α selection experiments reproducibly identify QTL, QTL not shared between the two mating types are likely false positives resulting from the small number of segregants within the mapping pool.